Cytotherapy. 2024 May 17:S1465-3249(24)00719-9. doi: 10.1016/j.jcyt.2024.05.012.
Online ahead of print.

Allogeneic stem cells engineered to release interferon β and scFv-PD1 target glioblastoma and alter the tumor microenvironment

Ioulia Vogiatzi [1], Lucia Moreno Lama [2], Amelia Lehmann [2], Filippo Rossignoli [2], Jan Gettemans [3], Khalid Shah [4]

Affiliations

PMID: 38852095 DOI: 10.1016/j.jcyt.2024.05.012

Abstract

Highly malignant brain tumors, glioblastomas (GBM), are immunosuppressive, thereby limiting current promising immunotherapeutic approaches. In this study, we created interferon receptor 1 knockout allogeneic mesenchymal stem cells (MSC) to secrete dual-function pro-apoptotic and immunomodulatory interferon (IFN) β (MSC^{KO}-IFNβ) using a single lentiviral vector CRISPR/Cas9 system. We show that MSC^{KO}-IFNβ induces apoptosis in GBM cells and upregulates the cell surface expression of programmed death ligand-1 in tumor cells. Next, we engineered MSC^{KO} to release a secretable single-chain variable fragment (scFv) to block programmed death (PD)-1 and show the ability of MSC^{KO}-scFv-PD1 to enhance T-cell activation and T-cell-mediated tumor cell killing. To simultaneously express both immune modulators, we engineered MSC^{KO}-IFNβ to co-express scFv-PD1 (MSC^{KO}-IFNβ-scFv-PD1) and show the expression of both IFNβ and scFv-PD1 in vitro leads to T-cell activation and lowers the viability of tumor cells. Furthermore, to mimic the clinical scenario of GBM tumor resection and subsequent treatment, we show that synthetic extracellular matrix (sECM) encapsulated MSC^{KO}-IFNβ-scFv-PD1 treatment of resected tumors results in the increase of CD4+ and CD8+ T cells, mature conventional dendritic cells type II and activation of microglia as compared to the control treatment group. Overall, these results reveal the ability of MSC^{KO}-IFNβ-scFv-PD1 to shape the tumor microenvironment and enhance therapeutic outcomes in GBM.

Keywords: IFNβ; checkpoint inhibitors; glioblastoma; immunomodulation; resection; scFv-PD1.